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INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Ahmad Y.	Sheikh	Pleasant Valley, WI
Thomas B.	Borchardt	Des Plaines, IL

☐ Additional inventors are being named on the ___ separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)
THE DESOLVATION/RECRYSTALLIZATION OF SOLVATES IN THE PHARMACEUTICAL INDUSTRY

CORRESPONDENCE ADDRESS

Direct all correspondence to:

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☒ Firm or Individual Name | Pharmacia Corporation
Address | Patent Department
Address | 800 N. Lindbergh Boulevard - 04B
City | St. Louis | State | MO | ZIP | 63167
Country | USA | Telephone | 314-694-6812 | Fax | 314-694-9095

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification *Number of Pages* 10
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☐ Application Data Sheet. See 37 CFR 1.76

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Respectfully submitted,

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TYPED or PRINTED NAME Kalim S. Fuzail

TELEPHONE 847-581-5247

REGISTRATION NO. (if appropriate) 45,805
Docket Number: 01013/1/US

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

PROVISIONAL UNITED STATES PATENT APPLICATION

for

THE DESOLVATION/RECRYSTALLIZATION OF SOLVATES IN THE PHARMACEUTICAL INDUSTRY

by

Ahmad Y. Sheikh and Thomas B. Borchardt

THE DESOLVATION/RECRYSTALLIZATION OF SOLVATES IN THE PHARMACEUTICAL INDUSTRY

Often, isolation of the desired crystalline form of an active pharmaceutical ingredient (API) goes through crystallizing a solvated or hydrated form of the compound. These forms are then transformed to desired solvent free forms through thermal treatment. This paper presents a theoretical framework to help develop scientifically well grounded and easy to implement strategies for robust performance during the desolvation and subsequent recrystallization of the solvated forms. The framework is comprised of Gibbs free energy temperature and composition temperature (solvent and compound) phase diagrams and also considers structural data on various polymorphs of the compounds. The utility of such diagrams in mechanistic understanding of complex and intertwined thermodynamic and kinetic events taking place during the desolvation/recrystallization process is discussed through two case studies, and simple and quick experiments to construct such diagrams for solvated forms with very different properties are identified. Translation of the theoretical framework for equipment design and process operation are also described and demonstrated for directing large scale manufacturing processes towards the isolation of thermodynamically meta-stable forms.

1. INTRODUCTION

A very significant fraction of all active pharmaceutical ingredients (API) are prepared in crystalline form for reasons related to stability and ease of handling during various stages of drug development. Often multiple crystalline forms, *i.e.*, polymorphs, solvates and hydrates exist for the API. Implications of polymorphism on properties such as dissolution rate and transport characteristics have resulted in significant emphasis on the characterization and control of the crystalline form of the API. Phase relationships between various polymorphic forms are best captured through phase diagrams.

Often, controlled isolation of the desired crystalline form of the API goes through crystallizing a solvated or hydrated form of the compound which is then transformed to the desired solvent free form through thermal treatment. Within the context of such desolvation/recrystallization processes, free energy-temperature (G-T) and composition temperature (x-T) phase diagrams are most fundamental in

developing a sound theoretical framework for the control of such processes. The G-T diagram, which is constructed by determing $2n$ properties of a polymorphic system comprised of n forms (Grunenberg *et al*, 1996), reveals two very significant practical aspects of the system *viz.*, whether the forms are monotropically or enatiotropically

5   related and if enantiotropically related where does the transition temperature lie. When drawn in sufficient detail, this diagram also quantifies the thermodynamic driving force for the interconversions between forms as a function of temperature. One of the protocols used in this paper to construct a G-T diagram also allows determination of how the transition temperature between the solvated and non-

10   solvated form varies with solvent activity. Two-component composition-temperature (x-T) diagrams are ideally suited for understanding phase transformations through de-solvation under conditions that include presence of solvent for systems involving solvates and hydrates (Morris *et al* (2001)). Regions of stability for each of the different phases are determined in the phase space from the transition temperatures

15   determined in the G-T diagram and determination of eutectic and more importantly peritectic points. The latter is defined as the temperature at which a solvate *is* in equilibrium with a non-solvated form in a saturated environment. Traversing the x-T diagram along solvent content and temperature axes help identify possible pathways to isolate different non-solvated forms. The desirable trajectories of temperature and

20   solvent content can then be implemented for controlled operation of de-solvation recrystallization processes.

In this paper two different approaches towards the construction of G-T and x-T phase diagrams are presented. These reflect the very distinct nature of the two multi solid-form systems (referred to as compounds A and B) that were the subject of

25   this research. The resulting framework for each of the systems is then used to identify "process related" strategies towards controlled isolation of the desired form. Results from successful implementation of these strategies at manufacturing scale are also presented.

2. G-T x-T FRAMEWORK FOR COMPOUND A

30   The polymorphic system for compound A is comprised of three non-solvated forms (referred to in this work as forms I, II and III) and one ethanol solvate (IV). The API was manufactured as form I through desolvation recrystallization of form IV. Whilst simple differential scanning calorimetry (DSC) is often sufficient to obtain $2n$

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parameters (for instance T_m and ΔH_{fus}), for compound A this was not possible because melting events were not observed for forms II and III due to phase conversion to form I. Furthermore, the propensity of compound A to readily solvate/hydrate in solvents made it very difficult to obtain desired thermodynamic properties from solubility measurements. An alternative approach based on eutectic melting (Yu *et al*, 2000) was employed to construct a G-T diagram for forms I, II and III. The peritectic point for completion of the x-T diagram was determined through DSC and hot-stage microscopy in a sealed environment.

Eutectics were formed between three reference compounds and each of the three non-solvated forms to determine heat of fusion and melting points through DSC. Table 1 summarizes the results for eutectic mixtures with forms I, II and III. The data were used to calculate free energy differences between the forms using equation 1.

$$x_{ej}(G_j-G_i)T_{ei} = \Delta Hm_{ej}(T_{ei}-T_{ej})/T_{ej} - \Delta C_{peij}[T_{ei}-T_{ej}-T_{ei}\ln(T_{ei}/T_{ej})] +$$
$$RT_{ei}\{x_{ej}\ln(x_{ej}/x_{ei}) + (1-x_{ej})\ln[(1-x_{ej})/(1-x_{ei})]\} \qquad (1)$$

where x_{ej} and x_{ei} are the mole fraction of polymorphs j or i in the eutectic; (G_j-G_i) is the free energy difference between polymorphs i and j; ΔHm_{ej} and ΔHm_{ei} are the enthalpy of eutectic melting; T_{ej} and T_{ei} are the temperatures of eutectic melting; ΔC_{peij} is the heat capacity change across the eutectic melt (determined from DSC baselines) and R is the ideal gas constant. The entropy difference for any given phase conversion was determined from the relationship between ΔG and T, and the transition temperature was then calculated using equation 2.

$$T_t = \Delta H/\Delta S \qquad (2)$$

The G-T plot (Figure 1a) showed that both forms II and III were enantiotropically related to the highest melting form (form I). Transition temperatures for II to I and III to I transformations were found to be very similar. This similarity was not surprising given the narrow enthalpy gap between forms II and III. The narrow enthalpy gap also made it difficult to ascertain which of these two forms was more stable at room temperature. It was therefore predicted that any attempts to selectively produce either of these forms through desolvation of IV would be very difficult.

DSC scans for form IV in a sealed pan showed an endotherm corresponding to its desolvation, immediately followed by an exotherm related to crystallization of

form III. These thermal events representing peritectic melting occurred over 70-110°C. This broad range was refined through hot-stage optical microscopy, which was conducted using high temperature silicon oil to mimic sealed conditions. Furthermore, a shallow temperature ramp of 1°C/min was used over the temperature

5   range of interest. Microscopy showed that true peritectic point was approximately 72°C. The peritectic point, along with the data from the G-T diagram were used to construct the x-T diagram shown in Figure 1b.

Table 1: Eutectic melting data for the polymorphs of compound A

Crystal Form	Form I	Form II	Form III
T_m, °C	274-276	Phase conversion	Phase conversion
RC=phenacetin, T_m 134.5°C			
X_e	0.25	0.25	0.25
T_e, °C (mean)	118.2	124.7	124.7
ΔH_{me}, (kJ/mole)	24.64	25.99	27.08
RC=benzanilide, T_m 163.0°C			
X_e	0.17	0.18	0.18
T_e, °C (mean)	155.6	156.6	156.2
ΔH_{me}, (kJ/mole)	28.32	31.95	31.42
RC=salophen, T_m 187.0°C			
X_e	0.42	0.42	0.42
T_e, °C (mean)	171.7	170.1	170.1
ΔH_{me}, (kJ/mole)	25.82	36.83	34.62

Figure 1: Semi-quantitative G-T and x-T diagrams for compound A

1a.

1b.
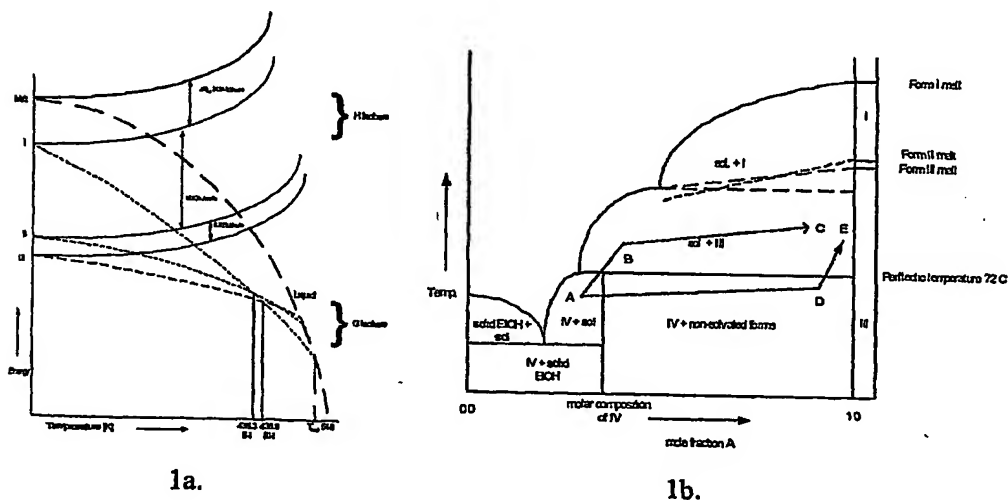
The x-T diagram identifies two routes for potential desolvation of form IV.

Route ABC is an environment with inadequate solvent removal. In this environment, the composition of the system does not change rapidly as a sample on the left hand side of the solvate composition line is heated. As the temperature reaches the peritectic point, form IV transforms into a non-solvated crystal form and a saturated solution of A. The initial form that results from desolvation could be a meta-stable form or the thermodynamically stable form at that temperature. As the system is heated further, the kinetic form would transform via solution mediated transformation to the thermodynamically stable form at that temperature (form III in this case). The free energy gap between II and III is, however, very small, and consequently mixtures of II/III could also be obtained. As more and more solvent is removed from the system above the peritectic, further transformations become extremely slow in the absence of solvent mediation.

An alternate route ADE, which requires very efficient solvent removal, proceeds in such a way that most of the excess solvent (more than what defines the solvate) is removed below the peritectic point. As a consequence, when the system crosses the solvate composition line, a solid-solid mixture of form IV and non-solvated form is produced. There is no solution in this mixture as the system is below the solidus. Further removal of solvent from within the solvate below the peritectic temperature transforms more form IV through solid-solid conversion to the non-solvated form. Under these circumstances, the most likely anhydrous form to crystallize would be the kinetically favored form – form I in this case. If the temperature were to exceed the peritectic point at this stage of drying, the anhydrous form crystallized below the peritectic may not convert to form III, again because solid-solid conversion would be the mechanism, which can be extremely slow. Whilst thermodynamic control for the crystallization of form I through form IV cannot be achieved below 164°C, a route akin to ADE offers the highest probability of success.

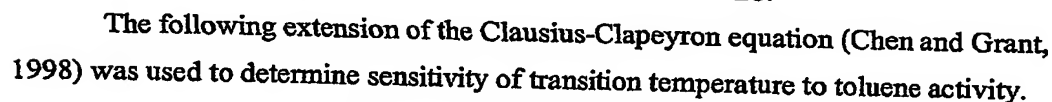### 3. G-T x-T FRAMEWORK FOR COMPOUND B

Compound B had three non-solvated forms (referred to in this work as I, II and III) and two toluene solvates (IV and V). API was manufactured through the de-solvation of form IV to I. DSC could not be used for quantitative purposes with this system because significant variations were observed in data for different lots of the same form. Most of the factors identified by Bettinetti et al (1999) for such variations

were prevalent in compound B. Solution calorimetry and intrinsic dissolution rate (IDR) measurements were used to determine $2n$ parameters for each of the five forms. Neat toluene was used as the solvent for solution calorimetry, while a 50/50 (v/v) toluene/heptane mixture was used in IDR experiments. The reason for using mixtures

5   for IDR was to reduce dissolution rates to an extent that they could be measured with some accuracy. While concentration vs time data were collected for ~2 hrs, only results from the first two minutes were used to determine IDR. Table 2 lists heat of solution and IDR for all the five forms.

Table 2: Heat of solution and IDR data for compound B

Form	Heat of solution kJ/mol	IDR $\mu g \ sec^{-1} \ cm^{-2}$
I	16.62	162.00
II	24.34	78.84
III	18.31	107.46
IV	25.56	83.96
V	16.14	127.34

10   A thermodynamic model similar to that of Gu and Grant (2001) was used to construct the G-T diagram shown in Figure 2a. Usage of solution calorimetry and IDR data was extremely beneficial within this model because it allowed inclusion of forms IV and V on the diagram. Transition temperatures between solvated and non-solvated forms on this diagram are by definition the same as peritectic points on an x-

15   T diagram. Determination of the peritectic points from the G-T diagram was particularly helpful for compound B, because low vapor pressure of toluene over the temperature range of interest made it impossible to find peritectic points using methods employed for compound A. The calculated peritectic was used to construct the x-T diagram with form IV shown in Figure 2b. While the G-T diagram unveiled

20   many interesting relationships, the most significant observation from desolvation of form IV to I was that these two forms were essentially monotropic, with form IV being more stable until its eutectic melting in toluene. As a consequence, only structural reasons related to formation of a solvent free lattice of form IV and its collapse into an anhydrous form could lead to the isolation of form I. On the x-T

25   diagram again two pathways i.e., ABC and ADE could be identified, with the isolation of form I most likely through a pathway akin to ADE.

Figure 2: Semi-quantitative G-T and x-T diagrams for compound B

2a.

2b.

The following extension of the Clausius-Clapeyron equation (Chen and Grant, 1998) was used to determine sensitivity of transition temperature to toluene activity.

$$a = \exp\left(\frac{\Delta H_{tr}}{nRT_{tr}} - \frac{\Delta H_{tr}}{nRT}\right) \qquad (3)$$

In the above equation, subscript tr stands for transition, ΔH for enthalpy difference between the two forms and n for number of moles of solvent in the solvate. Figure 3 shows the variation of the IV-II, IV-III and IV-V transition temperatures with toluene activity. The data showed that if toluene activity in the headspace were lower than the predicted value at any given temperature, the solvate would readily convert to the appropriate non-solvate. Conversely, if the toluene activity were higher than the predicted value at any given temperature, the solvate would remain stable.

Figure 3: Solvate-non solvate transition temperature vs solvent activity

4. PROCESS DESIGN IMPLICATIONS

For both compounds A and B, drying protocols reflective of pathway ADE

were developed and instituted. Features of these drying procedures included shallow temperature ramps and extremely efficient solvent removal through optimization of purge flowrate and strength of vacuum, especially below the peritectic point. While the latter was achieved with relative ease for compound A (peritectic temperature

5   ~72°C), for compound B (sub-ambient peritectic) almost all the excess solvent was removed through effective cake washes prior to subjecting the solids to heat. Successful implementation of these strategies resulted in significantly better control of solid form during the drying process.

5. CONCLUDING SUMMARY

10   Utility of a thermodynamic framework comprised of a G-T diagram in tandem with an x-T diagram is established for developing fundamental understanding of desolvation /recrystallization processes. Two different approaches reflective of the underlying nature of the polymorphic systems are presented for collecting the needed data to construct these diagrams. Usage of the framework to develop process designs

15   for the drying operations is discussed.

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WHAT IS CLAIMED IS:

1. A crystalline form of an active pharmaceutical ingredient substantially as disclosed herein.

2. A process for preparation of the crystalline form of claim 1 substantially as disclosed herein.

9

ABSTRACT

Utility of a thermodynamic framework comprised of a G-T diagram in tandem with an x-T diagram is established for developing fundamental understanding of desolvation /recrystallization processes. Two different approaches reflective of the

5   underlying nature of the polymorphic systems are presented for collecting the needed data to construct these diagrams. Usage of the framework to develop process designs for the drying operations is discussed.

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